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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,292	03/15/2001	Yoshimi Homma	31671-169944	7573

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EXAMINER	
GUNTER, DAVID R	
ART UNIT	**PAPER NUMBER**
1634	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/787,292	Applicant(s) HOMMA ET AL.	
	Examiner David R. Gunter	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *9-14, 17-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) ~~1-20~~ *1-8, 15, 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Specification

1. The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Claims

2. The claims in this application do not commence on a separate sheet in accordance with 37 CFR 1.52(b). Appropriate correction is required in response to this action.

3. The claims contain numerous minor informalities as an apparent result of the translation of the application into English. For example, in Claim 1, the phrase "specific region of genome DNA" should read "specific region of genomic DNA." The claims must be written in proper idiomatic English.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 2, and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

A "representative number of species" means that the species that are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus that embraces widely variant species cannot be achieved by disclosing only one species within the genus.

a. Regarding Claim 1, the claim recites a method for detecting "cell-proliferating diseases." The examples provided in the specification teach the use of the current method for the detection of psoriasis (figure 1, also page 13 lines 14-22) and chronic rheumatoid arthritis (page 17, lines 3-25). The genus of "cell-proliferating diseases" encompasses a broad range of diseases ranging from multiple types of solid tumors and leukemia to warts and gingival hyperplasia, each with a unique cause, pathology, method of treatment, and outcome. The two species taught in the instant application do not adequately represent the entire genus of cell-proliferating diseases because one of skill in the art would not have recognized other members of the highly variable genus bases solely on psoriasis and chronic rheumatoid arthritis.

Although methylation of DNA is known to be one important regulator of gene expression, it is by no means the only mechanism involved in gene regulation. In a similar manner, alterations in the expression of receptor genes have been shown to play a role in the pathogenesis of many diseases of cell proliferation, but changes in the level of expressed receptor is not the sole cause of diseases of cell proliferation and is not a consistent finding in all cell-proliferative diseases. Holzmann, et al., Anticancer Research 12:1013-1018, 1992 (hereinafter referred to as "Holzmann") determined the level of methylation of the erbB2 gene in cells taken from tumors of the colon and stomach. In tumor cells from the colon, "no significant difference in the banding pattern between tumor and mucosa samples was seen" (page 1014, right column, second paragraph; also figure 1). However, in "stomach tissues a clear difference in banding pattern between tumor and mucosa samples was noted" (page 1015, left column, second paragraph). These findings demonstrate a poor correlation between altered methylation

of a particular gene and a cell-proliferative disorder, and thus that there is substantial variation among members of the genus of "cell proliferative disorders."

Furthermore, even when alterations in the methylation level of a receptor gene are demonstrated, these changes do not necessarily correlate to a change in the expression of the receptor. Gamou, et al., Japanese Journal of Cancer Research 79:989-995, 1988 (hereinafter referred to as "Gamou") analyzed the methylation status of the epidermal growth factor receptor (EGFR) gene in five cell lines: two small cell lung carcinoma lines, two squamous cell carcinoma lines, and one adenocarcinoma line. Gamou found that "the 5' region is methylation-free regardless of the expression status of the EGFR gene" and that "gene methylation is not solely responsible for control of EGFR gene expression" (page 994, right column, lines 24-29).

Taken together, Holzmann and Gamou demonstrate that the methylation state of a particular receptor gene cannot be used as a test for the diagnosis of all diseases of cell proliferation. There is significant variation in the methylation level of receptor genes among proliferative diseases, and the finding of altered methylation does not accurately predict alterations in receptor expression. As such, the ability of the method of the instant application to detect the presence of two types of proliferative disease does not adequately demonstrate its ability to detect the presence of all cell proliferative diseases. In addition to enablement the first paragraph of 112 requires a "written description". As set forth by the Court in Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date the applicant was in possesstion of the claimed invention. For the reasons outlined above, possession has not been demonstrated.

b. Regarding Claims 1, 2, and 15 the claims recite a method of detecting cell-proliferating diseases characterized by determining the methylation level of cytosine residues within DNA involved in the expression of a "cytokine receptor gene." Cytokines represent a broad genus of molecules including interluekins, interferons, and white blood cell growth factors. The instant application teaches the use of the method to detect the methylation level of the gene for the receptor for Epidermal Growth Factor (EGFR; page 13, lines 14-22; also figure 1) and the epidermal growth factor-like receptor 2 (erbB2; page 15 lines 4-10; also figure 2). Epidermal growth factor is not a cytokine, but is classified as a hormone. Therefore EGFR and erbB2 are not members of the genus "cytokine receptor gene" and cannot adequately represent the entire genus of receptor genes.

The examiner has assumed for the purpose of prosecution that in the instant application the term "cytokine" is incorrectly used as synonymous with "hormone," such that Claims 1, 2, and 15 are intended to be read "DNA involved in the expression of a cytokine or hormone receptor gene." This use of the term "cytokine" further broadens the genus of "cytokine receptors" by incorporating the receptors for growth hormone, prolactin, the thyroid hormones T3 and T4, insulin, and a plurality of other ligands. EGF does not serve as an adequate representative of the genus "cytokine or hormone receptors" because these receptors vary in their function, tissue distribution, the mechanisms by which they bind their ligands, and the mechanisms by which they activate the cells in which they are found.

5. Claims 1, 3, 6, and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Regarding Claim 1, the phrase "determining the methylation level of cytosine residues" lacks antecedent basis because it is unclear how determining the methylation level of cytosine residues results in the diagnosis or detection of cell-proliferating disease. The claim should be amended to either include the additional method steps necessary to detect disease or to modify the preamble to remove the unclear terms.

b. Regarding Claim 3, the terms "epidermal growth factor receptor" (EGFR), "platelet derived growth factor receptor" (PDGFR), and "vascular endothelial cell growth factor receptor" (VEGFR) lack antecedent basis. Claims 1 and 2 recite that the DNA to be analyzed is a "cytokine receptor gene." Epidermal Growth Factor, Platelet Derived Growth Factor, and Vascular Endothelial Cell Growth Factor are considered to be hormones, not cytokines. As a result, EGFR, PDGFR, and VEGFR are hormone receptors and not cytokine receptors. Either EGFR, PDGFR, and VEGFR should be removed from Claim 3, or Claims 1 and 2 should be amended to provide appropriate antecedent basis for the specific receptors recited in Claim 3.

c. Regarding Claim 6, the term term "epidermal growth factor receptor" lacks antecedent basis. Claims 1 and 2 recite that the DNA to be analyzed is a "cytokine receptor gene," but EGFR is a hormone receptor and a not cytokine receptor. Either EGFR should be removed from Claim 6, or Claims 1 and 2 should be amended to provide appropriate antecedent basis for EGFR in Claim 6.

d. Regarding Claim 7, the Claim is vague and indefinite because the phrase "668th, 671st, 687th, and 697th cytosine residues in the nucleotide sequence" is unclear. It is not clear whether this terminology is meant to refer to the 668th residue of SEQ ID NO: 4,

which is a cytosine, or if the terminology is meant to refer literally to the 668th cytosine residue in SEQ ID NO: 4. SEQ ID NO: 4 is only 1200 nucleotides in length, and on visual inspection appears unlikely to contain 668 cytosine residues. Therefore, for the purpose of examination, the term "668th cytosine residue" will be interpreted to mean "residue 668." However, the claims should be amended to clarify this issue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-5, 15, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Gamou in light of Kaneko, et al., Japanese Journal of Cancer Research 76:1136-1140, 1985 (hereinafter referred to as "Kaneko"). Claims 1-5 of the instant application recite a method for the detection of cell-proliferating diseases characterized by determining the methylation level of cytosine residues located within the regulatory region of cytokine receptor genes. Claims 15-16 recite a plurality of methods for the detection of DNA methylation including the use of methylation-sensitive restriction enzymes.

Gamou discloses a method for determining the methylation level of cytosine residues of the regulatory region of the EGFR gene in samples taken four different types of lung carcinoma (page 990, left column, second paragraph through page 991, right column). Gamou further discloses the use of the methylation-sensitive restriction enzyme Hpa II (page 990, right column)

a. Regarding Claims 1, 2, and 15: as described in the section titled "Claim Rejections - 35 USC § 112" above, the recitation in Claims 1, 2, and 15 of "cytokine receptor" is not consistent with the specific receptors recited in Claims 3 and 6. The receptors of Claim 3 and 6 (EGFR, PDGFR, and VEGFR) are hormone receptors. For the purpose of examination, the phrase "cytokine receptor" of Claim 1, 2, and 15 will be interpreted to include hormone receptors such as those listed in Claims 3 and 6.

b. Regarding Claims 1 and 15, Gamou discloses the embodiment in which the methylation level of cytosine residues within the specific region of DNA involved in the expression of a cytokine receptor gene (EGFR, Page 990, right column, second paragraph).

c. Regarding Claim 2, Gamou teaches the embodiment in which the gene to be analyzed is a gene for a member of the tyrosine kinase receptor family (EGFR, page 990, left column).

d. Regarding Claim 3, Gamou teaches the embodiment in which the gene to be analyzed is the gene for EGFR (page 990, left column).

e. Regarding Claim 4, Gamou teaches the embodiment in which the cell proliferating disease is a solid tumor (lung carcinoma, page 990, left column).

f. Regarding Claim 5, Gamou teaches the embodiment in which the region to be analyzed is a region in a CpG island of the promoter or intron.

g. Regarding Claim 16, Gamou teaches the embodiment in which the method of detecting the level of methylation is a method using a methylation sensitive restriction enzyme (Hpa II, page 990, left column).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claim 6 rejected under 35 U.S.C. 103(a) as being unpatentable over Gamou in view of Ishii, et al. Proceedings of the National Academy of Sciences of the United States of America 82:4920-4924, 1985 (hereinafter referred to as "Ishii") in further view of Johnson, et al., The Journal of Biological Chemistry 263(12):5693-5699, 1988 (hereinafter referred to as "Johnson"). Claim 6 of the instant application recites the additional limitation to Claim 1 that the specific region of DNA to be analyzed is a region represented by the nucleotide sequence from residue 381 to residue 962 of SEQ ID NO: 4.

Gamou discloses the embodiment in which the methylation level of cytosine residues within the specific region of DNA involved in the regulation of expression of a cytokine receptor gene is determined (EGFR, Page 990, right column, second paragraph). Gamou further refers to an analysis of the published sequence of the EGFR (Ishii, page 4291, Figure 1) to locate CCGG motifs that may serve as sites for DNA methylation.

SEQ ID NO: 4 of the instant application is a 100% match to GenBank accession number M38425, identified as the 5' end of the human EGFR. This DNA fragment is well known in the art as a model system in which to study the regulation of EGFR (Johnson, page 5693, right column). It would have been obvious to one of ordinary skill in the art at the time the application was filed to apply the method of Gamou for the detection of DNA methylation to a known model of EGFR gene regulation in order to assess the potential role of methylation in the regulation of EGFR expression.

Allowable Subject Matter

Claims 7 and 8 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowed, however Claims 7 and 8 are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David R. Gunter whose telephone number is (703) 308-1701. The examiner can normally be reached on 9:00 - 5:00 M - F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-9212 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0198.

David R. Gunter, DVM, PhD
August 27, 2002

STEPHANIE W. ZITOMER
PRIMARY EXAMINER